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(71) Applicant *(for all designated States except US)*: A.C.R. APPLIED COATING RESEARCH S.A. [LU/LU]; 8, Boulevard Royal, L–2449 Luxembourg (LU).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: CILURZO, Francesco [IT/IT]; Via Pasubio, 6, I–20154 Milan (IT).

(74) Agent: GERVASI, Gemma; Notarbartolo & Gervasi S.p.A., Corso di Porta Vittoria, 9, I–20122 Milan (IT).

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(54) Title: COUMARIN–BASED OR MELILOT–BASED TRANSDERMAL PLASTERS

(57) Abstract

Transdermal plaster containing melilot or coumarin as the active ingredient, comprising: a) an impermeable substrate layer; b) an adhesive layer containing the active principle dispersed therein and containing as the adhesive polymer an acrylic polymer selected from the group consisting of: (I) a mixture of: the cationic copolymer (b–1) dimethylamino–ethyl–methacrylate / neutral ester of methacrylic acid with one or more C_1–C_{10} alcohols, the neutral copolymer (b–1–(i)) ethyl acrylate / methyl methacrylate, or else (II) an anionic copolymer (b–1(ii)) methacrylic acid / methyl methacrylate, said adhesive layer (b) moreover comprising the following components: b–2) glycerine, b–3) polyethylene glycol 400; c) a protective film which may be removed just before use.

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COUMARIN-BASED OR MELILOT-BASED TRANSDERMAL PLASTERS

Field of the invention

The present invention regards a transdermal plaster containing melilot or coumarin.

State of the art

Chronic venous insufficiency (CVI) is a physiopathological condition whereby the venous system is no longer able to perform its function adequately.

Two forms may be distinguished: relative and absolute.

The former manifests itself only in adverse functional and postural conditions, such as orthostatism; the latter manifests itself in any functional or postural condition.

CVI presents a clinical picture that comprises simple subjective manifestations of venous disease (heaviness around the ankles in orthostatism, especially at the start of the warm season, vague pain during micturition, at times accentuated in the premenstrual phase, evening suboedema). On this are inevitably superimposed, over time, infective processes, atrophy, eczema, sclerosis, pyodermatitis, and varicose ulcers.

CVI is a very frequent condition, which affects more prevalently women and is more widespread in the town than in the country.

In a fair number of cases, a certain family tendency has been identified, with a more likely transmission from mother to son or father to daughter, and it has been found that in approximately two thirds of the subjects with varicose veins there were precedents of familial varicose disease.

Varicose insufficiency is moreover favoured by the following conditions: prolonged orthostatism, prolonged sitting, heat, folds in clothing, use of very high-heeled shoes, and use of clothing that is too tight. Other predisposing factors may be obesity, gout, alcohol, and smoking.

To this, in the case of women, two particularly critical periods may be added: pregnancy and menopause. In addition, an unfavourable action is attributed to oestrogens on account of their action of distending elastic and muscular fibres of the walls of veins. Initial venous insufficiency is traditionally dealt with by applying hygienic rules, physical therapy and pharmacological treatment.

The hygienic rules consist in performing regular physical activity, sleeping with legs raised, and avoiding standing up for a long time, etc.

Physical treatment envisages the use of stockings and panty hoses for confining and exerting a compressive and graduated action of massage, as well as thermal balneotherapy, and in particular ozonized balneotherapy.

As far as pharmacological treatment of CVI is concerned, drugs having properties of reinforcing and protecting the veins and surrounding tissues are normally used. These drugs prove more effective if taken already in the initial phase of the illness, even though they do not constitute an alternative to the hygienic rules described above, rules which must in any case be scrupulously observed.

The drugs currently used may be classified, according to their pharmacodynamics, into endothelium-protective and phlebotonic drugs, even though frequently such a distinction is not clear, since the different molecules possess both these characteristics.

Finally, of consolidated use are anti-inflammatory drugs.

Extract of *Melilotus officinalis* contains a series of active principles, among which the following stand out for their therapeutic importance: flavonoid benzopyrones and coumarins. The former perform the types of activity already referred to as regards endothelium-protective and phlebotonic drugs. Of greater importance in terms of originality of mechanism of action and pharmacological effects is the coumarin component, it being the first substance available provided with specific anti-oedematigenous properties.

These properties are expressed through a dose-independent receptor-type mechanism by means of direct interaction with the smooth muscle of lymph vessels and with macrophages. In this way, the natural coumarin contained in the melilot extract has an action of stimulation of the draining of tissue liquids by the lymphatic route and of elimination by phagocytosis of proteic macromolecules.

"Trattamento farmacologico e/o balneoterapico dell'insufficienza venosa cronica" ["Pharmacological treatment and/or balneotherapy of chronic venous insufficiency"] Stefanini L., Gigli P., Galassi P., Pierallini F., Tillieci A.,

Scalabrino A., GAZZETTA MEDICA ITALIANA pp. 179-185 Vol.155 (August 1996) describes a preliminary clinical study on subjects affected by CVI to whom melilot was administered by oral route. From the results of this study it emerges that treatment with melilot proves on average favourable in the treatment of various manifestations of CVI, such as forms of paraesthesia, night cramp, and hypothermia, whereas it is particularly effective in the treatment of malleolar oedema, thanks to the anti-oedematigenous activity of the coumarin present therein.

Coumarin, and hence also melilot which contains it, presents a drawback in that it is poorly absorbed in oral administration on account of its ample first-pass effect. Its solubility in water is very low (0.22%), the apparent partition coefficient between *n*-octanol and the pH-7.4 buffer is rather high, the tendency to bind proteically is low (35%), and the half-life elimination time is 1 hour. These biopharmaceutical and pharmacokinetic parameters would appear to indicate that coumarin may be a good candidate for transdermal administration. Absorbability of coumarin by transdermal route has in fact been assessed by means of a pharmacological study by applying a cream containing 5% coumarin on the skin of rats. From this study it emerged that coumarin is substantially absorbed by topical administration, and that this absorption increases considerably as the surface of application increases: if an area of application of the cream measuring 30 cm^2 is used, there is an increase in bioavailability of 300% as compared to oral administration (W.A. Ritschel and S.A. Hussain "Transdermal Absorption and Topical Bioavailability of Coumarin" Meth. and Find. Exptl. Clin. Pharmacol. 1988, 10(3): 165-169).

Consequently, to obtain a degree of absorption of coumarin higher than the one obtained by oral administration, which, as has been seen above, is low, it is necessary to apply coumarin topically in the form of cream over a wide area of the body, and in any case, as acknowledged by the authors of the above study, even applying it over an area of 30 cm^2, absolute bioavailability reaches only 66% of the total. In addition, transdermal absorption using cream presents a series of drawbacks, such as lack of reproducibility, in particular on account of the poor control over the amount of cream on the surface of the skin on which it

is spread. It should also be added that it is not always pleasant for the person affected by chronic venous insufficiency to apply a cream that leaves visible residue on the skin in the area of application, which, in this case, as was noted above, must be very extensive for satisfactory results to be achieved.

For this reason, transdermal plasters containing coumarin have been studied. In particular, assessments have been made of the bioavailability of coumarin from transdermal plasters in which the adhesive layer containing the active principle was made up of a silicone elastomeric matrix which contained as permeability promoter glycolized ethoxylated glycerides, available on the market under the trade mark LABRAFIL®. With these plasters, it has been possible to increase absolute bioavailability to 71% ("Use of Sorption Promoters to Increase Systemic Absorption of Coumarin from Transdermal Drug Delivery Systems " W.A. Ritschel, J.K. Barkhaus" Arzn. Forsch. /Drug Res. 38(I), No.12 (1988) pp.1774-1777).

Another transdermal system in which the adhesive layer, represented by a silicone matrix containing different concentrations of a permeability promoter, such as propylene glycol, has shown that in a transdermal plaster containing 5% of coumarin and quite massive quantities of permeability promoter (30%), the maximum bioavailability achievable was 69.3% ("Evaluation *in vitro* and *in vivo* of dimethicone transdermal therapeutic systems. Influence of propylene glycol on drug release", Ritschel W.A., Nayak P.M. Arzn. Forschung (1987), 37(3) pp. 302-306).

To this may be added the fact that these plasters, in which the adhesive matrix is of a silicone type, present the disadvantage of requiring, for the preparation of the matrix, the exclusive use of organic solvents. In fact, however complete the process of drying of the matrix may be, there inevitably remain traces of solvent, which, in the case of organic solvents may create skin irritation, above all following upon a prolonged use of the plaster over time, as in the case of the treatment of CVI.

Technical problem

The need is felt of having available a coumarin-based or melilot-based transdermal plaster, whereby it is possible to obtain absorption of high

quantities of active principle (coumarin or melilot), and which can be prepared from water-based adhesive matrices, and hence a plaster that does not present the drawbacks of non-water-based adhesive matrices.

Summary of the invention

The applicant has now unexpectedly found the transdermal plaster according to the present invention, containing coumarin or melilot, thanks to which the amount of active principle absorbed through the human epidermis after 24 hours is between 15 and 25 $\mu g/cm^2$, corresponding to 80-100% of active principle contained in the plaster.

The transdermal plaster according to the present invention comprises in particular:

a) an impermeable substrate layer;

b) an adhesive layer containing the active ingredient dispersed therein and as the adhesive polymer an acrylic polymer selected from the group consisting of:

(I) a mixture of the cationic copolymer (b-1) dimethylamino-ethyl-methacrylate / neutral ester of methacrylic acid with one or more C_1-C_{10} alcohols and a the neutral copolymer (b-1-(i)) ethyl acrylate / methyl methacrylate;

or else:

(II) an anionic copolymer (b-1(ii)) methacrylic acid / methyl methacrylate;

said adhesive layer (b) moreover comprising the following components:

b-2) glycerine

b-3) polyethylene glycol 400

c) a protective film which may be removed just before use.

Description of the drawings

Figure 1 represents the quantity of melilot absorbed, expressed in $\mu g/cm^2$ per unit time (hours) with the plasters in which the adhesive layer was prepared, respectively, from compositions 7 and 10 given in Table 1.

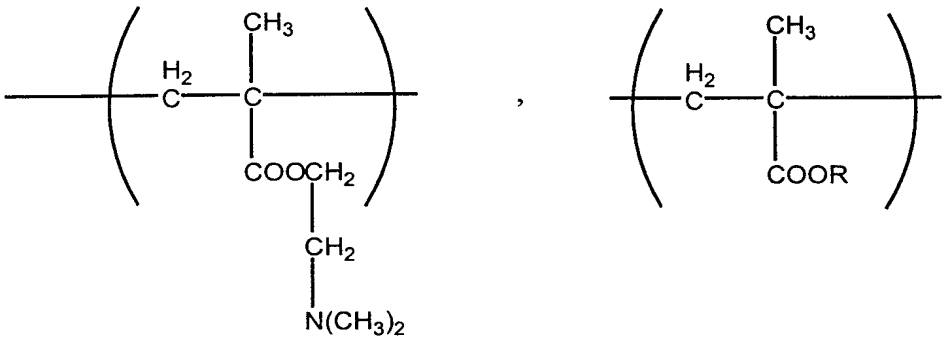
Figure 2 represents the amount of coumarin absorbed, expressed in $\mu g/cm^2$ per unit time (hours) with the plasters in which the adhesive layer was prepared, respectively, from compositions 9 and 11 given in Table 1.

Figure 3 represents the *in vitro* dissolution profile expressed in $\mu g/cm^2$ per unit

time, obtained with the coumarin-based and melilot-based plasters in which the adhesive layer was prepared, respectively, from formulations 7 and 9 given in Table 1.

Detailed description of invention

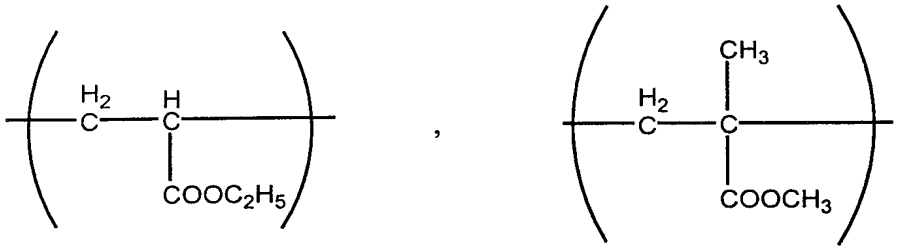
In the adhesive layer (b) of the plaster according to the present invention, the cationic acrylic copolymer, dimethylaminomethacrylate (b-1), preferably presents the following repetitive units:



where R = CH_3, C_4H_9.

It is moreover characterized by a mean molecular weight of 150 000. This type of polymer is in particular available on the market under the registered trade mark Eudragit ® E 100.

The copolymer (b-1(i)), which is possibly present in the adhesive layer according to the present invention and presents the following repetitive units:

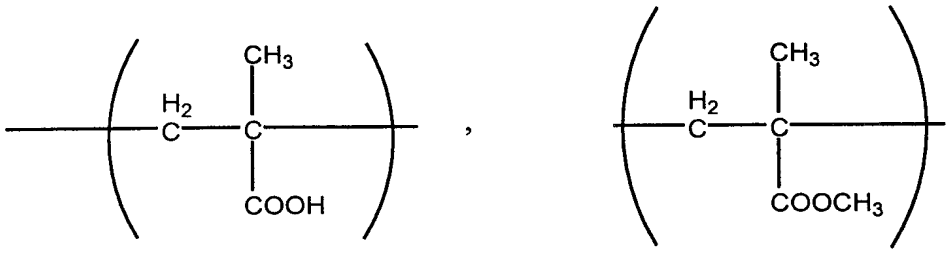


preferably has a mean molecular weight of around 800 000.

This copolymer is added in the form an aqueous dispersion in concentrations of 40% and has a viscosity of 33 mPa.s in the phase of preparation of the aqueous adhesive matrix used in the preparation of the adhesive layer of the plaster according to the present invention.

This type of aqueous dispersion is available on the market under the registered trade mark EUDRAGIT ® NE40D.

In the anionic copolymer, methacrylic acid-methyl methacrylate (b-1-(ii)), possibly used in the adhesive layer of the plaster according to the present invention, the repetitive units



are preferably in a weight ratio of 1:1, and the mean molecular weight of the polymer is approximately 135 000. This copolymer is available on the market under the registered trade mark EUDRAGIT ®L100.

When the adhesive layer of the plaster according to the present invention contains the mixture of cationic copolymer (b-1) and neutral copolymer (b-1-(i)), as well as comprising glycerol (component (b-2)) and polyethylene glycol 400 (PEG 400, component (b-3)), it preferably contains also C_8-C_{20} saturated fatty acids and/or C_2-C_6 bicarboxylic acids. According to a particularly preferred embodiment, these acids are chosen from the group consisting of: lauric acid, succinic acid, adipic acid or their mixtures.

In a particularly preferred embodiment of the transdermal plaster according to the present invention, the adhesive layer (b) contains:

- melilot in concentrations of between 1 and 4% by weight, even more preferably between 1.4 and 2% by weight, or coumarin in concentrations of between 0.15 and 0.8% by weight, even more preferably 0.25-0.5% by weight, with respect to the total weight of the adhesive layer;
- the polymer (b-1) in concentrations of between 20 and 60% by weight, even more preferably between 31 and 32% by weight, with respect to the total weight of the adhesive layer;
- the polymer (b-1-(i)) in concentrations of between 10 and 50% by weight, even more preferably between 33 and 34% by weight, with respect to the total weight of the adhesive layer;
- glycerol in concentrations of between 7 and 13% by weight, even more

preferably between 10 and 10.5% by weight, with respect to the total weight of the adhesive layer;

- PEG 400 in concentrations of between 1 and 7% by weight, even more preferably in a concentration of 4% by weight, with respect to the total weight of the adhesive layer;
- lauric acid in concentrations of between 13 and 17% by weight, even more preferably in a concentration of 15% by weight, with respect to the total weight of the adhesive layer;
- succinic acid in concentrations of between 0.1 and 0.5% by weight, even more preferably in a concentration of 0.3% by weight, with respect to the total weight of the adhesive layer;
- adipic acid in concentrations of between 2 and 7% by weight, even more preferably in concentrations of between 3.5 and 4.5% by weight, with respect to the total weight of the adhesive layer.

When the adhesive layer of the plaster according to the present invention contains only the anionic copolymer (b-1-(ii)), the adhesive layer also contains sodium hydroxide to neutralize the carboxyl groups present in the said copolymer.

In a particularly preferred embodiment of the transdermal plaster of this type, the adhesive layer contains:

- melilot in concentrations of between 1 and 4% by weight, even more preferably between 1.4 and 2% by weight, or coumarin in concentrations of between 0.15 and 0.8% by weight, even more preferably 0.25-0.5% by weight, with respect to the total weight of the adhesive layer;
- the anionic acrylic copolymer (b-1-(ii)) in concentrations of between 10 and 40% by weight, even more preferably of between 15 and 20% by weight;
- sodium hydroxide in concentrations of between 2 and 4% by weight, even more preferably in concentrations of between 3 and 3.5% by weight;
- PEG 400 in concentrations of between 20 and 35% by weight, even more preferably in concentrations of between 25 and 29% by weight;
- glycerine in concentrations of between 10 and 14% by weight, even more preferably of between 11 and 13% by weight.

The adhesive layer may possibly contain thickening agents, such as hydroxypropyl methylcellulose with various values of viscosity, and other excipients of a conventional type, such as polyvinyl pyrrolidone, etc.

The applicant has found that the plasters according to the present invention, characterized in that they contain the polymeric mixture (b-1)+(b-1-(i)), or else the anionic copolymer (b-1-(ii)), present good adhesive properties. As emerges from the examples given hereinafter, the coumarin-based or melilot-based transdermal plaster the adhesive layer of which contains only the cationic copolymer (b-1), or the acrylic polymer of 2-ethyl-hexyl-acrylate, which is used in the phase of preparation of the adhesive composition in the form of an aqueous dispersion available on the market under the name UCECRYL M808, do not possess sufficient adhesive properties (Formulation 14 given in Table 1).

In addition, the transdermal plasters according to the present invention present the indisputable advantage that the adhesive matrix is prepared using water as main solvent, with consequent considerable advantages both as regards the economy of the process and as regards environmental pollution in the phase of drying of the adhesive matrix, and finally also for the patient who uses these plasters.

The plaster according to the present invention can be prepared using techniques of a conventional type.

Particularly preferred is the process that comprises the following stages:

A) forming the aqueous adhesive matrix containing the polymeric mixture (b-1)+(b1-(i)) or the anionic copolymer (b-1(i)), coumarin or melilot, glycerol (b-2), and polyethylene glycol 400 (PEG 400 (b-3));

B) spreading the aqueous matrix obtained in stage (A) on the chosen substrate (a); or

B') alternatively, spreading the adhesive matrix obtained in stage (A) on the protective film;

C) drying the material coming from stage (B) or stage (B') at a temperature of between 50 and 80°C in an air-circulation oven for a period of between 10 and 30 minutes;

D) applying the substrate layer (a), on which the adhesive layer (b) coming from

stage (C) is laid, to the removable protective film (c); or

D') applying the protective film (c), on which the adhesive layer (b) coming from the drying stage (C) is laid, to the substrate layer (a).

Stage (A) is preferably carried out as described in the examples, according to Method 2 exemplified as follows, in the case the adhesive layer contains the mixture of the cationic acrylic copolymer (b-1), in particular when the latter is Eudragit ® E100, and of the neutral acrylic copolymer (b-1-(i)), as well as in the preferred case where the latter is Eudragit® NE40D.

Stage (A) is instead preferably carried out according to Method 3 exemplified as follows, in the case where the adhesive layer contains only the anionic acrylic copolymer (b-1-(ii)), and the latter is, in particular, Eudragit ®L100.

The material of the substrate layer (a) of the plaster according to the present invention is selected from among the materials normally used in the preparation of transdermal plasters. Preferably, it is selected from the group consisting of: artificial silk with rayon-acetate fibres having a thickness of between 70 and 150 μm, polyurethane having a thickness of between 15 and 150 μm, polyester having a thickness of between 15 and 150 μm, polyether blocked with polyamide having a thickness of between 15 and 150 μm, polyether-urethane having a thickness of between 15 and 150 μm, and polyvinyl chloride having a thickness of between 15 and 150 μm.

The material used for the removable protective film is of the sort normally used for this purpose, such as siliconized paper.

The following examples of preparations of the transdermal plasters according to the present invention are reported hereinbelow, which are given purely to provide non-limiting illustrations. Also presented are the permeability tests, the peel tests, and the *in vitro* dissolution profile.

EXAMPLES

1) PREPARATION OF THE ADHESIVE MATRICES

The compositions of the adhesive matrices prepared are given in Table 1 below. The quantities are expressed in grams.

TABLE 1

No.	MEL	CUM	E100	L100	NE40D	MC808	GL	GP	PEG400	LA	SU	AD	NaOH	H_2O	ETOH
1	0.61	-	15	-	-	-	4.8	-	2.83	7.2	-	1.7	-	67.8	
2	0.63	-	15.4	-	-	-	5	-	-	7.5	-	1.8	-	69.8	-
3	0.62	-	15.4	-	-	-	3	-	2.48	7.1	-	1.9	-	69.6	-
4	0.64	-	15.1	-	-	-	4.9	-	1.94	7.3	0.2	1.8	-	68.3	-
5	0.63	-	10.6	-	29.6	-	3.4	-	1.4	5.1	0.1	1.2	-	47.9	-
6	0.47	-	10.9	-	28	-	3.5	-	1.4	5.3	0.1	1.3	-	49.1	-
7	0.7	-	10.8	-	29.7	-	3.5	-	1.4	5.2	0.1	1.3	-	49	-
8	-	0.17	15.1	-	-	-	4.9	-	2	7.3	0.2	1.8	-	68.6	-
9	-	0.17	10.9	-	28.1	-	3.5	-	1.4	5.3	0.1	1.3	-	49.37	-
10	1.28	-	-	14.8	-	-	9.7	-	22.2	-	-	-	2.7	49.4	-
11	-	0.22	-	15	-	-	9.8	-	22.5	-	-	-	2.7	49.4	-
12	0.85	-	13.9	-	-	-	-	8.6	-	5.7	2.6	1.7	-	28.8	37.4
13	0.85	-	13.9	-	-	-	-	8.6	-	5.7	2.6	1.7	-	28.8	37.4
14	0.99	-	-	-	-	99	-	-	-	-	-	-	-	-	-

MEL = melilot, e.s. extract; CUM = coumarin, E100: Eudragit ®E100, L100 = Eudragit ®L100, NE40D = Eudragit® NE40D, MC808 = Uceryl MC808, GL= glycerine, GP = propylene glycol; PEG 400 = polyethylene glycol 400, LA = lauric acid, SU = succinic acid, AD = adipic acid, EtOH = ethanol 95°.

Compositions 1-4 and 8 were prepared according to Method 1;

Formulations 5-7 and 9 were prepared according to Method 2;

Formulations 10 and 11 were prepared according to Method 3;

Formulations 12 and 13 were prepared according to Method 4; and finally, Formulation 14 was prepared according to Method 5.

METHOD 1

Lauric acid, adipic acid, succinic acid and Eudragit ® E 100 are added to water kept at a temperature of 80°C. The dispersion is stirred at 150 r.p.m. for 1 hour in vacuum conditions (-50 cmHg), using a mixer with spiral agitator. The solution obtained is cooled down to a temperature of 60°C, and then the mixture of glycerine and PEG 400 is added, and everything is kept under agitation in vacuum conditions.

The polymeric mixture is kept stirred for a further 20 minutes at 70 r.p.m. and is cooled to room temperature. At the end of cooling, the melilot or coumarin is added, and the mixture is stirred for 30 minutes at 100 r.p.m. under vacuum conditions (-60 cmHg). The polymeric mixture thus obtained is left to rest for at least 12 hours before proceeding to the preparation of the plaster.

METHOD 2

Lauric acid, adipic acid, succinic acid and Eudragit ® E100 are added to water kept at a temperature of 80°C. The dispersion is stirred at 150 r.p.m. for 1 hour in vacuum conditions (-50 cmHg), using a mixer with spiral agitator. The solution obtained is cooled down to a temperature of 60°C, and then the mixture of glycerine and PEG 400 is added, and everything is kept under agitation in vacuum conditions.

The polymeric mixture is kept stirred for a further 20 minutes at 70 r.p.m. and is cooled to room temperature. At the end of cooling, the melilot or coumarin is added, and the mixture is stirred for 30 minutes at 100 r.p.m. under vacuum conditions (-60 cmHg). To the dispersion thus obtained is added Eudragit ® NE40D, stirring again for 30 minutes at 100 r.p.m. under vacuum conditions (-60 cmHg). The polymeric mixture thus obtained is left to rest for at least 12 hours before proceeding to the preparation of the plaster.

METHOD 3

Eudragit ® L 100 is dispersed in 50% of the water used under stirring at 150 r.p.m. for 10 minutes. A solution of sodium hydroxide is prepared separately, dispersing the soda in the remaining fraction of water.

The sodium hydroxide solution, cooled to room temperature is added very rapidly to the suspension of Eudragit ® in water and stirred at 150 r.p.m. until a clear solution is obtained. After a further 10 minutes of stirring, PEG 400 and glycerine are added. The melilot and coumarin are added to the dispersion obtained, and the mixture is stirred for 30 minutes under vacuum conditions (-30 cmHg). The polymeric mixture obtained is left to rest for at least 12 hours, before proceeding to the preparation of the plaster.

METHOD 4

Lauric acid, adipic acid, succinic acid and Eudragit ® E100 are added to alcohol, and the dispersion is stirred at 150 r.p.m. for one hour, using a mixer with spiral agitator.

Water and propylene glycol are added under stirring to the solution obtained. The polymeric mixture is kept under agitation for a further 20 minutes at 70 r.p.m. in vacuum conditions (-50 cmHg). Next the melilot or coumarin is added, and the mixture is stirred for 30 minutes at 100 r.p.m. in vacuum conditions (-60 cmHg). The polymeric mixture obtained is left to rest for at least 12 hours, before proceeding to the preparation of the plaster.

METHOD 5

The melilot or coumarin is added to the Ucecryl MC808 and is stirred for 30 minutes at 100 r.p.m. in vacuum conditions (-60 cmHg). The polymeric mixture obtained is left to rest for at least 12 hours, before proceeding to the preparation of the plaster.

PREPARATION OF THE PLASTERS

The plasters are prepared by spreading the polymeric mixture constituting the matrix on the chosen substrate and by subsequent drying of the polymeric matrix or, as an alternative method, are spread on the protective film and attached, after drying to the substrate.

In both cases the operating conditions are as follows:

Rate of spreading: 1-2.5 m/min,

Thickness of spreading: 100-500 μm,

Temperature of drying: 50-80°C,

Circulation of air: 50-150 m^3/min.

DETERMINATION OF ADHESIVENESS

This determination was made by conducting the "Peel adhesion 180°C test" (PSTC -1; Pr En AFERA 4001, 1994), using a very high-precision mechanical dynamometer (Acquati mod. A10l, Arese, Italy).

Preparation of the samples

The samples to be analysed were taken one week after preparation of the plaster. The samples, which measured 2.5 x 20 cm, adhered to the plate and were subsequently subjected to a constant force of 20 N per cm of width, by rolling a 5-kg roller over them 5 times.

Operating conditions

- peeling angle: 180°C
- peeling rate: 300 m/min.

The force is expressed in cN/cm; for each sample three determinations were made.

The mean value for the adhesive plaster, the adhesive layer of which was obtained from formulation 7, was 440 ± 20 cN/ cm.

The values of adhesiveness of the other plasters were of the same order of magnitude as the value given above.

However, only the plasters the adhesive layer of which was prepared using formulations 7 and 9-11, showed satisfactory cohesive properties, and consequently the profile of permeability of the human epidermis for melilot or coumarin was assessed in these plasters.

PERMEABILITY TESTS

The tests for permeability of the human epidermis for the active principle were conducted using the modified Franz cell method.

The epidermis was obtained by separating the derma by treatment in water at

60°C for 1 minute. After drying, the human epidermis was kept in a refrigerator at 4°C. Before use, it was re-hydrated in physiological solution at room temperature for 16 hours. The cells used were modified Franz cells thermostatted at 37°C, so as to maintain the epidermis at a temperature of 32°C. As acceptor medium a pH 7.4 phosphate buffer solution (PBS) was used, degassed and sterilized by filtration with a 0.22-μm filter.

The antimicrobic agent used was streptomycin sulphate (0.01% w/v). The samples (200 μl each), were taken after 1, 3, 5, 7 and 24 hours. After each sampling, the receiving phase was re-integrated with the same solution used as fresh acceptor medium.

The quantitative determination was made by HPLC.

As is evident from Figures 1 and 2, the amount of active principle absorbed by the human epidermis after 24 hours was between 15 and 25 $\mu g/cm^2$, corresponding to 80-100% of the content of the plaster.

DETERMINATION OF RELEASE *IN VITRO*

The determination of release *in vitro* was made according to the extraction-cell method (in European Pharmacopoeia (1997) pp. 131-133).

The 4.9-cm^2 samples were placed on the substrate with the surface of release turned upwards and protected with a previously hydrated Cuprophan® membrane.

Operating conditions:

- temperature: 32 ± 0.5°C
- speed of rotation: 50 r.p.m.
- receiving phase: pH 4.5 acetate buffer
- volume of receiving phase: 500 ml
- volume taken in each sample: 10 ml
- sampling times: 0.5, 1, 2, 3, 4, 5, 6, 7, 8, and 24 hours.

The samples were analyzed via HPLC.

Each value is the mean obtained on 6 samples.

The results of this test are given in Figure 3 as regards the plasters the adhesive layer (b) of which was obtained respectively from formulations (7) and (9), from which it emerges that the dissolution *in vitro* of coumarin or melilot is between 20

and 25 $\mu g/cm^2$, corresponding to 90-100% of the amount of active principle contained in the plaster.

CLAIMS

1. Transdermal plaster containing melilot or coumarin as the active ingredient, comprising:

a) an impermeable substrate layer;

b) an adhesive layer containing the active ingredient dispersed therein and as the adhesive polymer an acrylic polymer selected from the group consisting of:

(I) a mixture of: the cationic copolymer (b-1) dimethylamino-ethyl-methacrylate / neutral ester of methacrylic acid with one or more C_1-C_{10} alcohols, the neutral copolymer (b-1-(i)) ethyl acrylate / methyl methacrylate,

or else

(II) an anionic copolymer (b-1(ii)) methacrylic acid / methyl methacrylate,

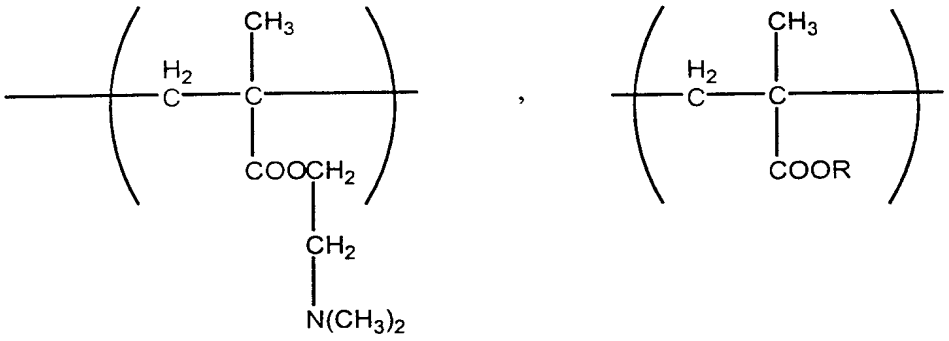
said adhesive layer (b) moreover comprising the following components:

b-2) glycerine

b-3) polyethylene glycol 400

c) a protective film which may be removed just before use.

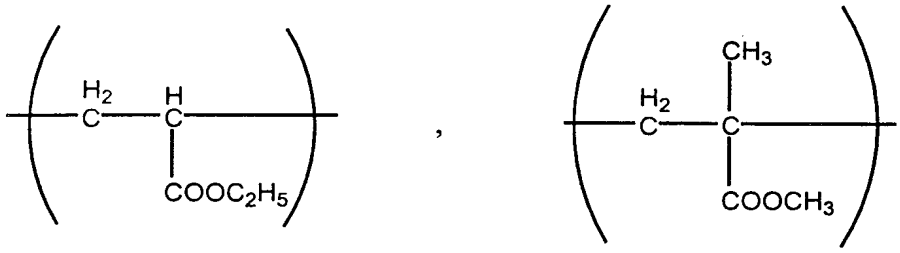
2. Transdermal plaster according to Claim 1, characterized in that the cationic acrylic copolymer dimethylaminomethacrylate (b-1) presents the following repetitive units:



where R = CH_3, C_4H_9

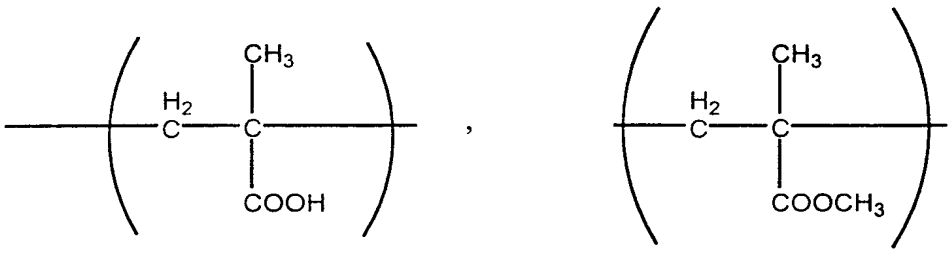
and a mean molecular weight of 150.000.

3. Transdermal plaster according to either of Claims 1 or 2, characterized in that the copolymer (b-1-(i)) that presents the following repetitive units:



has a mean molecular weight of around 800 000.

4. Transdermal plaster according to either of Claims 1 or 2, characterized in that, in the anionic copolymer methacrylic acid - methylmethacrylate (b-1-(ii)), the repetitive units



are in a weight ratio of 1:1 and the mean molecular weight of this polymer is approximately 135 000.

5. Transdermal plaster according to Claim 1, characterized in that when the adhesive layer contains the mixture of copolymer (b-1) and of copolymer (b-1-(i)), it further comprises C_8-C_{20} saturated fatty acids and/or C_2-C_6 bicarboxylic acids.

6. Transdermal plaster according to Claim 5, characterized in that these acids are chosen from the group consisting of: lauric acid, succinic acid, adipic acid or their mixtures.

7. The transdermal plaster according to Claim 1, characterized in that the adhesive layer (b) comprises:

- melilot in concentrations of between 1 and 4% by weight, or coumarin in concentrations of between 0.15 and 0.8% by weight, with respect to the total weight of the adhesive layer;
- the polymer (b-1) in concentrations of between 20 and 60% by weight, with respect to the total weight of the adhesive layer;
- the polymer (b-1-(i)) in concentrations of between 10 and 50% by weight, with respect to the total weight of the adhesive layer;

- glycerol in concentrations of between 7 and 13% by weight, with respect to the total weight of the adhesive layer;
- PEG 400 in concentrations of between 1 and 7% by weight, with respect to the total weight of the adhesive layer;
- lauric acid in concentrations of between 13 and 17% by weight, with respect to the total weight of the adhesive layer;
- succinic acid in concentrations of between 0.1 and 0.5% by weight, with respect to the total weight of the adhesive layer;
- adipic acid in concentrations of between 2 and 7% by weight, with respect to the total weight of the adhesive layer.

8. The transdermal plaster according to Claim 7, characterized in that the adhesive layer (b) comprises:

- melilot in concentrations of between 1.4 and 2% by weight, or coumarin in concentrations of between 0.25 and 0.5% by weight, with respect to the total weight of the adhesive layer;
- the polymer (b-1) in concentrations of between 31 and 32% by weight, with respect to the total weight of the adhesive layer;
- the polymer (b-1-(i)) in concentrations of between 33 and 34% by weight, with respect to the total weight of the adhesive layer;
- PEG 400 in a concentration of 4% by weight, with respect to the total weight of the adhesive layer;
- glycerine in concentrations of between 10 and 10.5% by weight, with respect to the total weight of the adhesive layer;
- lauric acid in a concentration of 15% by weight, with respect to the total weight of the adhesive layer;
- succinic acid in a concentration of 0.3% by weight, with respect to the total weight of the adhesive layer;
- adipic acid in concentrations of between 3.5 and 4.5% by weight, with respect to the total weight of the adhesive layer.

9. The transdermal plaster according to Claim 1 characterized in that when the adhesive layer (b) contains the anionic copolymer (b-1-(ii)) the adhesive layer

contains also sodium hydroxide to neutralize the carboxyl groups present in that copolymer.

10. The transdermal plaster according to Claim 1 characterized in that the adhesive layer contains the following components:

- melilot in concentrations of between 1 and 4% by weight or coumarin in concentrations of between 0.15 and 0.8% by weight, with respect to the total weight of the adhesive layer;
- the anionic acrylic copolymer (b-1-(ii)) in concentrations of between 10 and 40% by weight, with respect to the total weight of the adhesive layer;
- sodium hydroxide in concentrations of between 2 and 4% by weight, with respect to the total weight of the adhesive layer;
- PEG 400 in concentrations of between 20 and 35% by weight, with respect to the total weight of the adhesive layer;
- glycerine in concentrations of between 10 and 14% by weight, with respect to the total weight of the adhesive layer.

11. The transdermal plaster according to Claim 10, characterized in that the adhesive layer contains the following components:

- melilot in concentrations of between 1.4 and 2% by weight or coumarin in concentrations of between 0.25 and 0.5% by weight, with respect to the total weight of the adhesive layer;
- the anionic acrylic copolymer (b-1-(ii)) in concentrations of between 15 and 20% by weight, with respect to the total weight of the adhesive layer;
- sodium hydroxide in concentrations of between 3 and 3.5% by weight, with respect to the total weight of the adhesive layer;
- PEG 400 in concentrations of between 25 and 29% by weight, with respect to the total weight of the adhesive layer;
- glycerine in concentrations of between 11 and 13% by weight, with respect to the total weight of the adhesive layer.

12. The transdermal plaster according to any one of Claims 1-11, characterized in that it contains thickening agents.

13. The transdermal plaster according to any one of Claims 1-12, characterized in

that the material of the substrate layer (a) is selected from the group consisting of: artificial silk with rayon-acetate fibres having a thickness of between 70 and 150 μm, polyurethane having a thickness of between 15 and 150 μm, polyester having a thickness of between 15 and 150 μm, polyether blocked with polyamide having a thickness of between 15 and 150 μm, polyether-urethane having a thickness of between 15 and 150 μm, and polyvinyl chloride having a thickness of between 15 and 150 μm.

14. Process for preparing the transdermal plaster according to Claim 1, comprising the following stages:

A) forming the aqueous adhesive matrix containing the polymeric mixture (b-1)+(b1-(i) or the anionic copolymer (b-1(i)), coumarin or melilot, glycerol (b-2), and polyethylene glycol 400 (PEG 400 (b-3));

B) spreading the aqueous matrix obtained in stage (A) on the chosen substrate (a); or alternatively

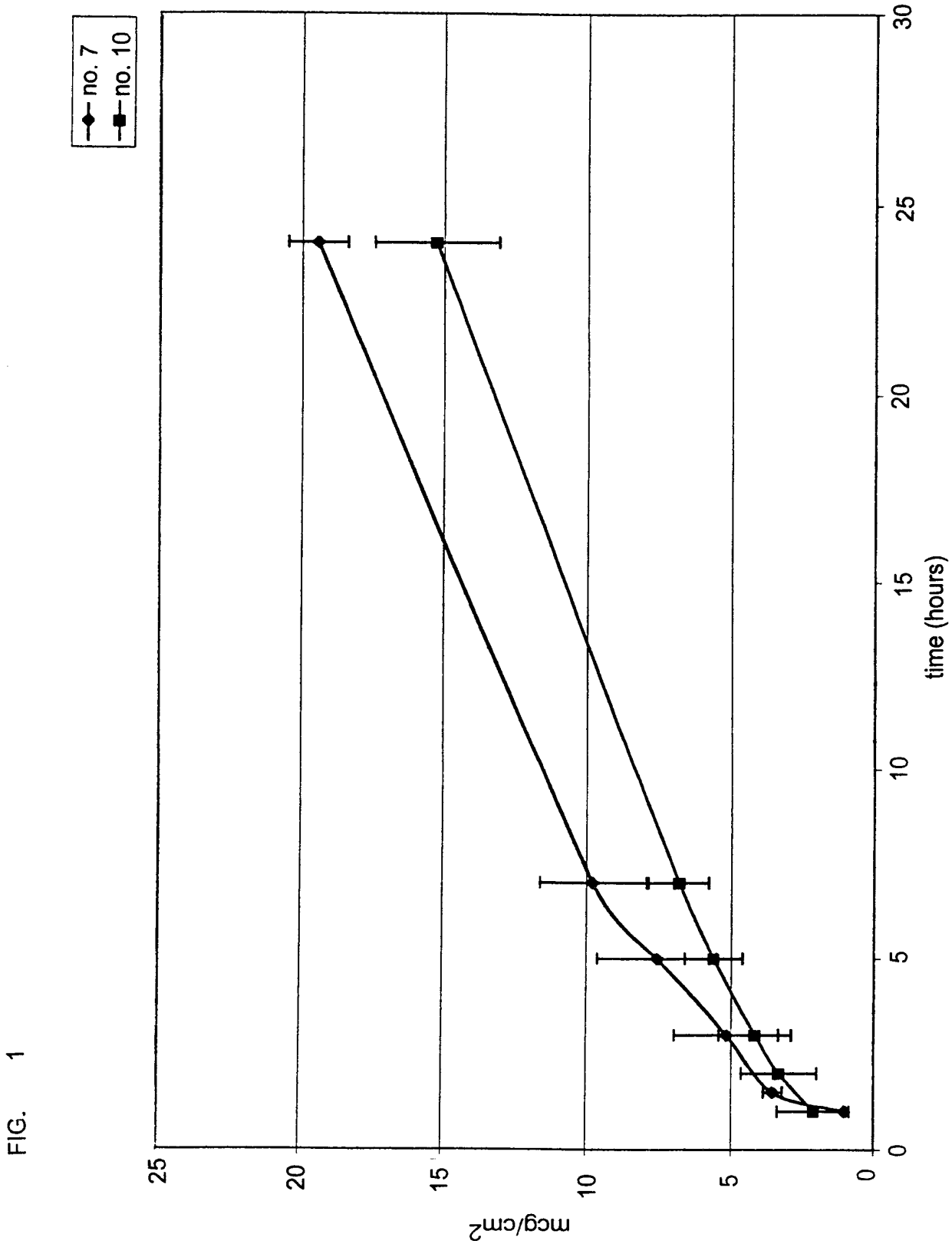
B') spreading the adhesive matrix obtained in stage (A) on the protective film;

C) drying coming from stage (B) or stage (B') at a temperature of between 50 and 80°C in an air-circulation oven for a period of between 10 and 30 minutes;

D) applying the substrate layer (a), on which the adhesive layer (b) coming from stage (C) is laid, to the removable protective film (c); or alternatively

D') applying the protective film (c), on which the adhesive layer (b) coming from the drying stage (C) is laid, to the substrate layer (a).

FIG. 1



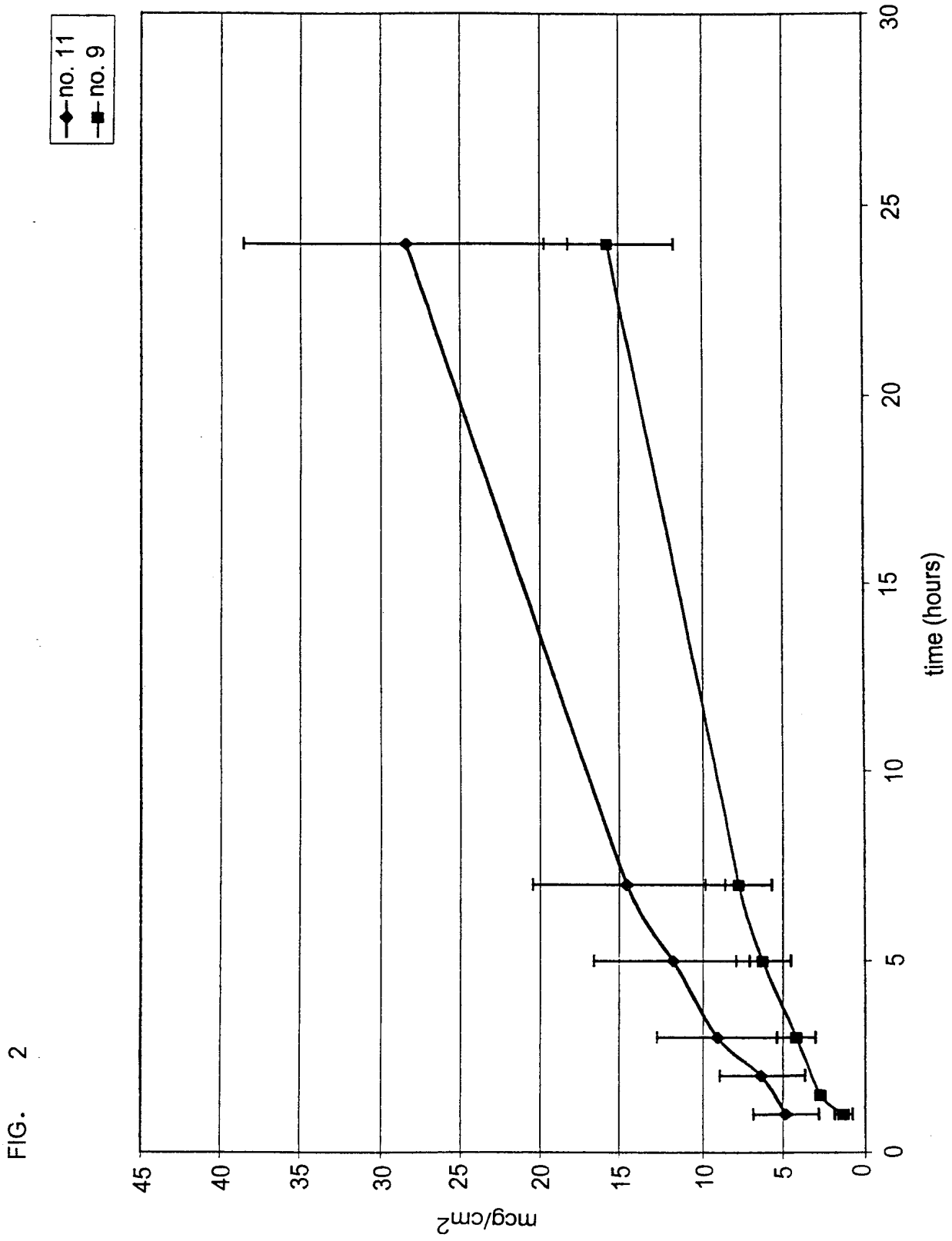


FIG. 2

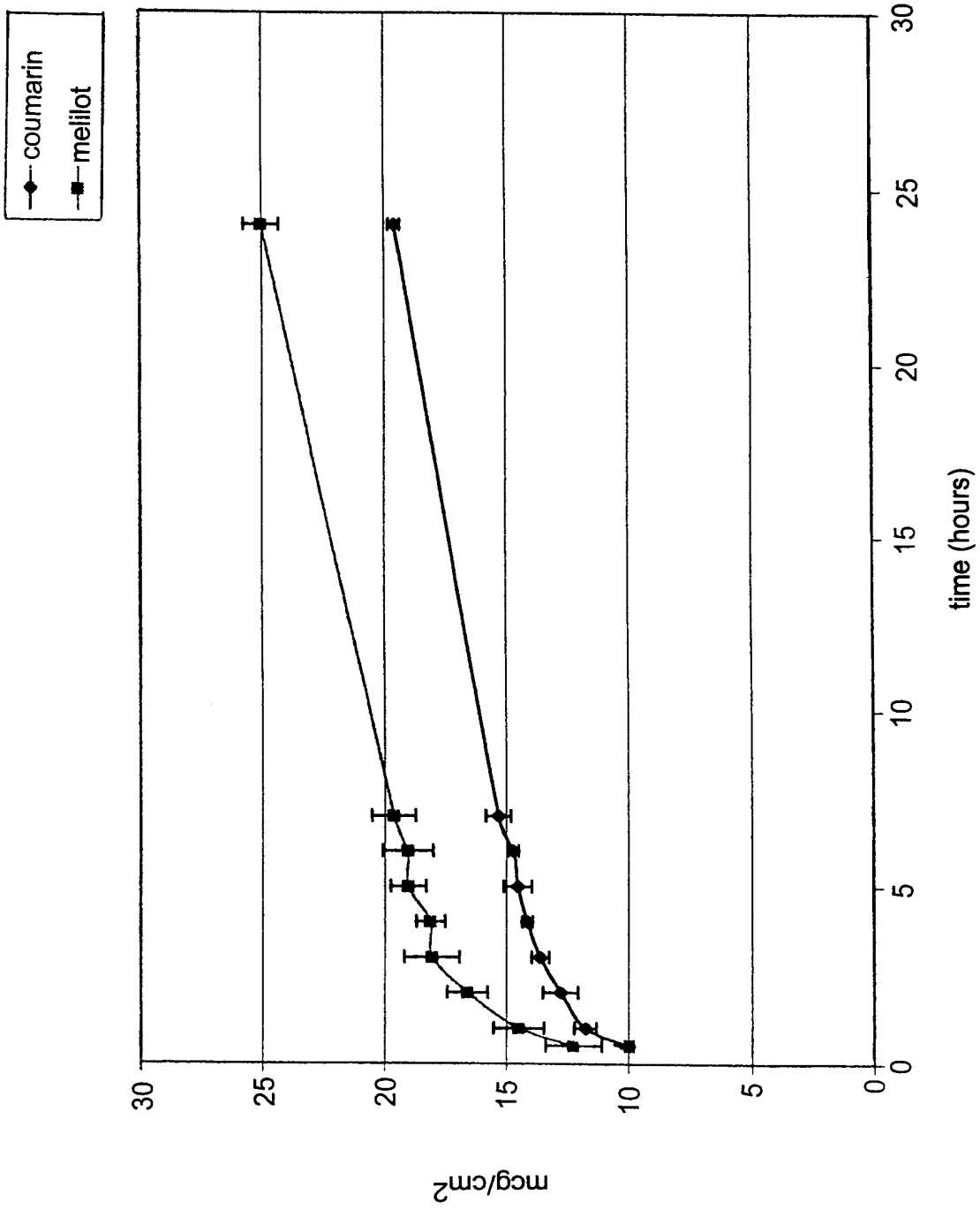


FIG 3

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/EP 99/07528

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L15/44 A61L15/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 750 139 A (CIERPKA HENNING F ET AL) 12 May 1998 (1998-05-12) examples tables 3-5 claims	1-8, 12-14
Y	US 5 133 970 A (ROTH ERNA ET AL) 28 July 1992 (1992-07-28) column 3, line 23 - line 38 examples claims	1-8, 12-14
A	US 5 730 999 A (LEHMANN KLAUS ET AL) 24 March 1998 (1998-03-24) column 3, line 32 -column 4, line 36 examples 1-9 tables 3-5 claims	1-8, 12-14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
11 February 2000	22/02/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Thornton, S

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INTERNATIONAL SEARCH REPORT

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PCT/EP 99/07528

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 296 512 A (BEIER HELMUT ET AL) 22 March 1994 (1994-03-22) examples 1-3,5 claims	1,2,4, 7-14
A	LIN SHAN-YANG ET AL: "The effect of plasticizers on compatibility, mechaincal properties, and adhesion strength of drug-free Eudragit E films" PHARMACEUTICAL RESEARCH,US,NEW YORK, NY, vol. 8, no. 9, September 1991 (1991-09), pages 1137-1143-1143, XP002107579 ISSN: 0724-8741 the whole document	1-8,12, 13
A	DATABASE WPI Section Ch, Week 198518 Derwent Publications Ltd., London, GB; Class A96, AN 1985-108347 XP002130393 & JP 60 053150 A (NITTO ELECTRIC IND CO), 26 March 1985 (1985-03-26) abstract	1
A	WO 85 03865 A (CASLEY SMITH JOHN ROYLE) 12 September 1985 (1985-09-12) page 1 -page 2 claims	1

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/EP 99/07528

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5750139 A	12-05-1998	AU 1221395 A	31-08-1995
		BR 9500681 A	24-10-1995
		CA 2142315 A	19-08-1995
		CN 1113434 A	20-12-1995
		CZ 9500350 A	18-10-1995
		EP 0668074 A	23-08-1995
		FI 950737 A	19-08-1995
		HU 72887 A	28-06-1996
		JP 8034729 A	06-02-1996
		NO 950605 A	21-08-1995
		PL 307326 A	21-08-1995
		ZA 9501111 A	16-10-1995
US 5133970 A	28-07-1992	DE 3924393 A	31-01-1991
		AT 115615 T	15-12-1994
		DD 296694 A	12-12-1991
		DE 59007998 D	26-01-1995
		DK 415055 T	20-02-1995
		EP 0415055 A	06-03-1991
		HU 54063 A	28-01-1991
		JP 3066775 A	22-03-1991
		KR 150001 B	01-10-1998
US 5730999 A	24-03-1998	DE 4310012 A	29-09-1994
		EP 0617972 A	05-10-1994
		HU 69378 A	28-09-1995
		JP 6305953 A	01-11-1994
US 5296512 A	22-03-1994	DE 3913734 A	31-10-1990
		DD 293835 A	12-09-1991
		EP 0394956 A	31-10-1990
		HU 53925 A	28-12-1990
		JP 2302486 A	14-12-1990
JP 60053150 A	26-03-1985	NONE	
WO 8503865 A	12-09-1985	AU 575930 B	11-08-1988
		AU 4114485 A	24-09-1985
		EP 0172893 A	05-03-1986
		US 5096887 A	17-03-1992